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Serum Zinc Correlates with Parent- and Teacher-Rated Inattention in Children with Attention-Deficit/Hyperactivity Disorder

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Abstract

Objective:

The aim of this study was to explore the relationship of zinc nutrition to the severity of attention-deficit/hyperactivity disorder (ADHD) symptoms in a middle-class American sample with well-diagnosed ADHD. Previous reports of zinc in ADHD, including two positive clinical trials of supplementation, have come mainly from countries and cultures with different diets and/or socioeconomic realities. Method: Children 5–10 years of age with DISC- and clinician-diagnosed ADHD had serum zinc determinations and parent and teacher ratings of ADHD symptoms. Zinc levels were correlated (Pearson's and multiple regression) with ADHD symptom ratings. Results: Forty-eight children (37 boys, 11 girls; 33 combined type, 15 inattentive) had serum zinc levels with a median/mode at the lowest 30% of the laboratory reference range; 44 children also had parent/teacher ratings. Serum magnesium levels were normal. Nutritional intake by a parent-answered food frequency questionnaire was unremarkable. Serum zinc correlated at $r = -0.45$ ($p = 0.004$) with parent-teacher-rated inattention, even after controlling for gender, age, income, and diagnostic subtype, but only at $r = -0.20$ ($p = 0.22$) with CPT omission errors. In contrast, correlation with parent-teacher-rated hyperactivity-impulsivity was nonsignificant in the opposite direction. Conclusion: These findings add to accumulating evidence for a possible role of zinc in ADHD, even for middle-class Americans, and, for the first time, suggest a special relationship to inattentive symptoms. They do not establish either that zinc deficiency causes ADHD nor that ADHD should be treated with zinc. Hypothesis-testing clinical trials are needed.

Introduction

Attention-deficit/hyperactivity disorder (ADHD) is the most-common serious childhood mental disorder, often persisting through adolescence and adulthood. It is characterized by inattention, distractibility, overactivity, and impulsivity excessive for developmental age, beginning by age 7, causing impairment in more than one setting, and not better explained by another disorder (APA 1994). It can be chronically impairing, especially without treatment.

As is true for most disorders, the available well-documented treatments, including medications having U.S. Food and Drug Administration (FDA)-approved indications (stimulants and atomoxetine) and behavioral treatment, are not fully effective for all patients. Although stimulants for ADHD are among the best documented and most-effective medications in psychiatry, the usually quoted response rate is approximately 2 of 3 for one stimulant tried, and 85%–90% for two tried in succession (e.g., Spencer et al. 1996; Arnold 2000). The newest

ADHD medication, atomoxetine, may improve the overall medication response rate by providing an additional option but is not expected to increase the normalization rate to 100%.

Although much has been discovered about the etiology, pathogenesis, and treatment of ADHD, much is still in doubt, and the myriad scientific threads weave a complex tapestry that, at times, seems to hide more than it reveals. One of the areas coming under increasing scrutiny is the role of nutrition. Of particular interest is zinc nutrition, implicated in numerous reports, mostly from outside the United States.

Zinc deficiency has been identified in children from many parts of the world, especially in newly developing countries (Hambidge 2000; Prasad 1996). In the United States, severe zinc deficiency does not seem common among healthy children. However, a more subtle deficiency state may be. This state, sometimes called *marginal zinc deficiency*, has been identified by a number of studies, including studies of children from middle-income families (Hambidge 2000; Prasad 1996). Marginal zinc deficiency is also generally noted in nutrition texts (e.g., Wardlaw and Kessel 2002). Although its prevalence has not yet been studied, it is believed to be widespread.

Zinc in ADHD

Zinc in serum, red cells, hair, and/or urine has been repeatedly reported significantly ($p < 0.001$) lower in ADHD compared to controls (e.g., Kozielec et al. 1994; Toren et al. 1996; Starobrat-Hermelin 1998; Arnold et al. 1990, Arnold 2000; Ward et al. 1990; Ward 1997), though most samples were not American (raising questions about dietary differences), and it is not clear how rigorously the diagnoses were made. Bekaroglu et al. (1996) reported mean serum zinc of 60.6 ± 9.9 mcg/dL in 33 boys and 15 girls with ADHD, compared to 105.8 ± 13.2 mcg/dL in healthy volunteers (30 boys and 15 girls) and concluded, “. . . zinc deficiency may play a role in aetiopathogenesis of ADHD.”

Akhondzadeh et al. (2004) reported that on the DuPaul ADHD rating scale, Turkish children assigned to methylphenidate (MPH) plus supplemental zinc improved significantly more than those assigned to MPH plus placebo by parent ($p < 0.05$) and teacher ($p = 0.04$) ratings. Bilici et al. (2004) reported that Iranian children with ADHD randomized to zinc monotherapy with 150 mg zinc sulfate/day for 12 weeks (above the recommended upper tolerable limit) improved twice as much as those assigned to placebo ($p < 0.002$). Because of differences in endemic diet, it is not clear how applicable such Mid-Eastern findings are to American children with ADHD. More extensive details can be found in the companion review article (Arnold and DiSilvestro, 2005).

Eight of 9 published samples reporting zinc data in ADHD were from outside the United States. We report in this paper new zinc data on a fresh sample of rigorously diagnosed American middle-class children.

Method

Serum zinc levels were collected from 48 children (37 boys and 11 girls), 5–10 years of age, being screened for a clinical trial of a nonzinc dietary supplement, with institutional review board (IRB)-approved informed consent and assent. Forty-four of these children also had parent and teacher ratings of ADHD symptoms on a 0–3 metric. Subjects were required to be in a stable medical condition during the 4 weeks immediately prior to initial screening, as demonstrated by medical history and physical examination; they could not have used any specialized diet or dietary supplement or investigational medication to treat or manage ADHD in the month prior to

screening; could not be currently using any psychoactive medication; and could not have a psychiatric disorder other than externalizing disorder requiring acute treatment.

Measures

All measures were collected before randomization to treatment. Serum zinc levels were determined in micrograms/deciliter through the university clinical reference laboratory for routine zinc assays.

Behavioral ratings for 44 of the children were obtained from parent and teacher on the Conners Rating Scales—Revised, long form (Conners 2001) prior to any treatment within the trial and while blind to serum zinc levels. On these scales, ratings of symptoms and other problems were made on a 0–3 metric from “not at all” to “very much.” The 18 *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (DSM-IV) symptoms of ADHD were extracted from this longer scale as being the most relevant. These were divided into the nine inattention symptoms and the nine hyperactivity-impulsivity symptoms. Each cluster of nine was averaged to derive item means, which were averaged across informants (parent and teacher) for each child.

Another measure was the Conners Continuous Performance Test (CPT; Conners 2000), from which omission errors were selected as representative of inattention and commission errors as representative of hyperactivity-impulsivity.

The Food Frequency Questionnaire (Jain et al. 1996) collected information about dietary habits. The data about average food intake per month, week, and day was analyzed by the Minnesota Nutrition Data System (University of Minnesota) to derive average daily intake of specific nutrients.

Data analysis

The descriptive data were averaged or counted and tabulated. Using SPSS for PC, the serum zinc levels were correlated (Pearson’s) with, respectively, mean inattention ratings (by parent and teacher averaged), mean hyperactivity-impulsivity ratings, CPT omission errors, and CPT commission errors. With four exploratory analyses, the significance level was set at $p = 0.05/4 = 0.012$ (two-tailed) for each test.

Because ADHD symptom ratings and CPT performance are known to vary by age, gender, and socioeconomic status, these potential confounders were entered into a multiple regression with zinc levels and each of the ADHD measures, along with diagnostic subtype, to check for possible alternative explanations of any significant correlation found.

Results

Sample characteristics

All 48 children met DSM-IV diagnostic criteria for ADHD, either inattentive ($n = 15$) or combined ($n = 33$) type, by parent-informant Diagnostic Interview Schedule for Children (DSM-IV version), confirmed by child psychiatrist interview and clinical review. The sample was mainly middle and upper class, with many professional parents, who responded to an ad for a trial of a dietary supplement (not zinc) for ADHD. Serum lead levels, collected simultaneously with zinc levels, ranged from less than 1 to 3 mcg/dL (reference range up to 9). Two children had a history of asthma. Other sample characteristics are shown in Table 1. Highlights of the nutritional profile of the sample, taken from the Food Frequency Questionnaire filled out by

parents, are shown in Table 2. The intake of all nutrients, including zinc, was estimated by parental report to be solidly in the adequate range.

<i>Characteristic</i>	<i>Count (%) or mean \pm sd</i>
Age, years	7.6 \pm 1.8
Male	37 (77%)
Caucasian	43 (90%)
Height (inches)	50.7 \pm 3.9
Weight (pounds)	63.8 \pm 15.3
CDC Age Norms	
Height for age (z-score)	0.1 \pm 1.0
Weight for age (z-score)	0.4 \pm 0.9
ADHD	
Inattentive type	15 (31%)
Combined type	33 (69%)
Oppositional-defiant disorder	6 (13%)
Other comorbidity	12 (25%)
Previous ADHD medication	8 (17%)
Other medications	22 (46%)
Multivitamins	10 (21%)
9 DSM-IV inattentive symptoms (0-3 scale; <i>n</i> = 44)	
Parent	2.3 \pm 0.57
Teacher	2.2 \pm 0.63
9 hyperactive/impulsive symptoms (<i>n</i> = 44)	
Parent	1.9 \pm 0.75
Teacher	1.6 \pm 0.87
CGI-S (1-7 scale)	4.6 (moderate-marked)

Table 1. Sample Profile (N = 48)

CGI-S = clinical global impression—severity; ADHD = attention-deficit/hyperactivity disorder; CDC = Centers for Disease Control.

	<i>Mean \pm sd</i>	<i>Percent of DRI^b</i>
Energy (kcal)	2027.4 \pm 634.4	107 ^c
Protein (gm)	78.7 \pm 29.0	328
Fat (gm)	78.7 \pm 29.0	NA
Carbohydrates (gm)	259.8 \pm 90.5	200
Calcium (mg)	1178.0 \pm 585.5	122 ^d
Iron (mg)	14.4 \pm 5.1	160
Magnesium (mg)	289.8 \pm 104.4	175
Zinc (mg)	11.4 \pm 4.3	190

Table 2. Mean Daily Intake of Some Key Nutrients by the Children in the Sample (5-10 Years of Age) From Food Frequency Questionnaire^a

^aThe Food Frequency Questionnaire was adapted from adult use with special instructions for parents about portion size and may have slightly overestimated actual daily intake.

^bDaily Reference Intake (DRI) presents Recommended Dietary Allowances (RDAs) and Adequate Intakes (AIs). RDAs and AIs may both be used as goals for individual intake (Institute of Medicine 2002). Percent of DRI calculated using RDA amounts, unless otherwise noted.

^cEstimated Energy Requirement (EER) available to calculate percentage (American Academy of Pediatrics 2003).

^dAI available to calculate percentage.

Serum zinc profile

Figure 1 shows the distribution of serum zinc levels relative to the laboratory reference range. The distribution favors the lower end of the reference range. Most of the sample (33 of 48) cluster in the lower half (88 or below) of the reference range (66–110), and over half the sample are in the lowest third. The median and mode (79) are at the lowest 30% of the 66–110 reference range. These figures probably underestimate the actual degree of marginal zinc nutrition in this population because serum zinc can be transiently elevated by one recent (within a day) high-zinc meal (Sandstead and Alcock 1997; Thompson 1991; Prasad 1993). This distribution of zinc levels contrasts with other important serum minerals drawn at the same time: Magnesium, calcium, and sodium levels were all either within the reference range or high; potassium was above the reference range in 6 of 48 cases and below in 1 of 48 cases. Besides zinc, only chloride tended low, with 12 of 48 below the reference range, all not clinically significant.

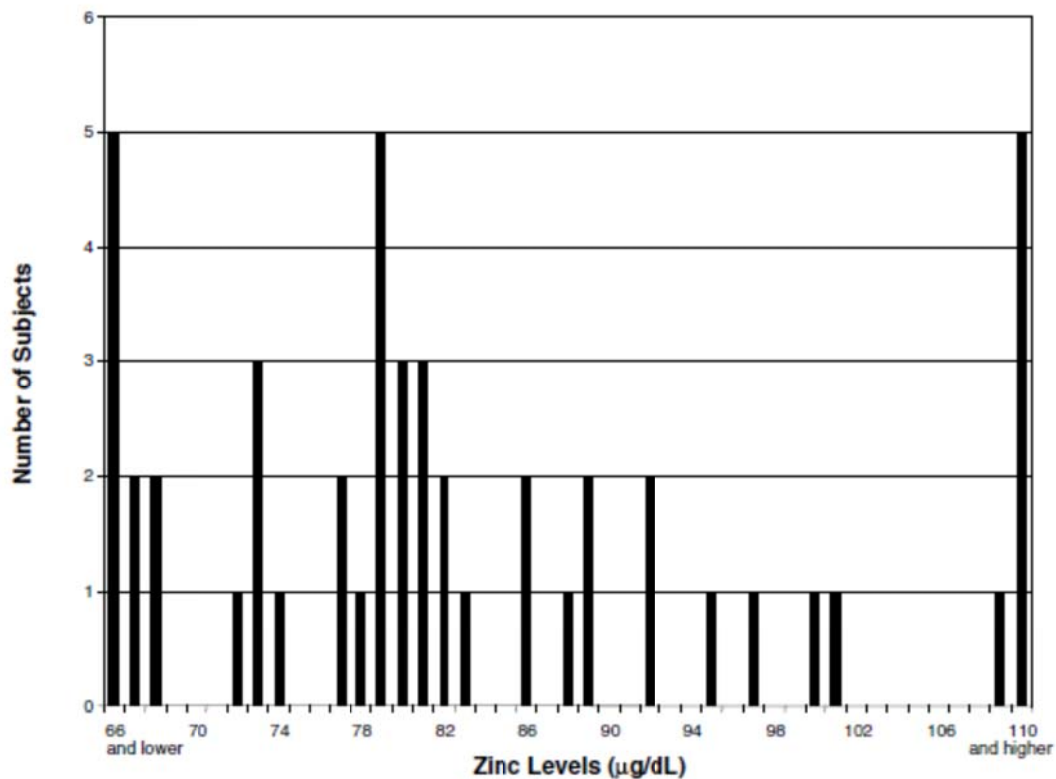


FIG. 1. Serum zinc levels in 48 children 5–10 years of age with ADHD. This lab’s reference range is 66–110 mcg/dL. The bars at 66 and 110 (extremes of the range) include both those with 66 or 110 and outliers beyond them. ADHD = attention-deficit/hyperactivity disorder.

Correlations with behavioral and cognitive measures

The 44 children (of these 48) for whom concomitant parent and teacher ratings were available showed a highly significant ($p = 0.002$; 2-tailed) inverse Pearson’s correlation ($r = -0.45$) of serum zinc with parent/teacher ratings of inattention: The nine DSM-IV inattentive symptoms rated on a 0–3 metric, averaged for parent and teacher. Thus, lower zinc levels were associated with greater parent- and teacher-rated inattention. In contrast, correlation of serum zinc with parent/teacher ratings of hyperactive-impulsive symptoms of ADHD was unimpressive, nonsignificant, and even in a *positive* direction ($r = 0.14$; $p = 0.35$). Thus, in this middle-class sample, there is a pattern of specific linkage of serum zinc level to a measure of

inattention rather than impulsiveness-hyperactivity. Although CPT omission errors (presumed to reflect inattention) were not significant, what tendency they did show was modestly ($r = -0.20$; $p = 0.20$) in the same direction as parent and teacher ratings of inattention, in contrast to CPT commission errors, presumed to reflect impulsiveness ($r = 0.03$; $p = 0.86$).

To check the possibility that the significant correlation of zinc level with inattention ratings could result from a confound of both variables with age, gender, socioeconomic status, or diagnostic subtype, we also correlated zinc levels with age ($r = 0.02$; $p = 0.9$), gender ($p = 0.27$), and diagnostic subtype ($p = 0.79$) and entered these variables and census tract median income into a multiple regression with zinc levels and each measure of ADHD severity (Table 3). The results did not detect any confounds with age, gender, family income, or diagnostic subtype. The association of zinc level with inattention ratings after adjustment for these potential confounders was still -0.446 ($p = 0.004$).

Discussion

The data reported here add more information to the accumulating evidence of a role for zinc nutritional state in the expression of ADHD symptoms. The results are very compatible with previous reports of low zinc levels in ADHD (Kozielec et al. 1994; Bekaroglu et al. 1996; Toren et al. 1996; Starobrat-Hermelin 1998; Arnold et al. 1990; Ward et al. 1990; Ward 1997). Because this sample was American middle- and upperclass children with ADHD rigorously diagnosed by accepted research standards, it addresses criticisms of previous reports concerning geographic and cultural differences in diet and questionable diagnosis. In addition, this is, to our knowledge, the first report of correlations of baseline serum zinc with the severity of ADHD symptoms. Such correlation is compatible with the reports by Ward (1990, 1997) that behavior deteriorated with the lowering of zinc levels by a food-dye challenge.

	<i>Parent/teacher inattention (n = 44)</i>		<i>Parent/teacher hyperactive impulsive (n = 44)</i>		<i>Continuous performance task omissions (n = 43)</i>		<i>Continuous performance task commissions (n = 43)</i>	
	β	p	β	p	β	p	β	p
Age	0.17	0.280	-0.16	0.18	-0.13	0.43	-0.01	0.97
Sex ^a	0.08	0.600	0.08	0.50	-0.01	0.93	0.31	0.07
Income ^b	-0.14	0.360	0.07	0.57	-0.16	0.33	-0.20	0.22
Subtype ^c	0.10	0.510	0.62	0.00	-0.153	0.36	0.01	0.94
Zinc	-0.45	0.004	0.13	0.26	-0.20	0.22	0.10	0.54

Table 3. Multiple Regression Adjustment for Four Possible Confounders of the Correlation Between Serum Zinc and Measures of Inattention and Impulsiveness

Note: The standardized beta coefficients in the zinc row may be compared to the uncontrolled Pearson's r correlations in the text.

β = Standardized Coefficient

^a Positive correlation indicates more association with males.

^b Income: Family median income of census tract.

^c Positive correlation indicates more association with combined type. Significant association of hyperactive-impulsive ratings with combined type compared to inattentive type is expected a priori.

If the finding of selective association of serum zinc levels with inattention rather than with hyperactivity-impulsivity is upheld by further study, including a more comprehensive evaluation of zinc status, it could have interesting implications for etiological diagnosis and treatment. This pattern (specific linkage of serum zinc level to measures of attention rather than impulsiveness or hyperactivity) suggests that zinc supplementation might help attentional symptoms, which are the most persistent of the ADHD symptoms, the most troublesome in adulthood, and, often, the hardest to treat.

However, the Turkish trial (Bilici et al. 2004) suggested the opposite: That zinc supplementation might help hyperactivity and impulsivity but not inattention. This discrepancy could result from chance or from differences in diet between Turkey and the United States, differences in sampling approach (Bilici's sample was quasiepidemiologic, screening all the local schools but excluding comorbidity), socioeconomic differences, differences in genetic basis for ADHD, difference in instruments (Bilici used a 52-item clinician instrument his group developed), age differences (Bilici's sample was older), the high dropout rate of the Turkish trial (only 193 of the 618 consented eligible subjects completed), or the high dose used in the Turkish trial. Perhaps the high doses of zinc sulfate (150 mg/day) used by Bilici et al. negated attentional/learning benefit while improving hyperactivity/impulsivity, even though, at lower levels, zinc might be more related to inattentive symptoms. It is also important to note that the results reported in this paper were naturalistic untreated correlations in contrast to the Turkish results from a randomized clinical trial. Therefore, we cannot rule out a paradox in which, for unknown reasons, serum zinc correlates with untreated inattention, but zinc supplementation only helps hyperactive-impulsive symptoms with which zinc level does not correlate naturalistically. The explanation can only be found by further study. We are undertaking studies to test the effect of RDA/RDI zinc supplementation, with and without stimulant, in a well-characterized American sample.

It is puzzling that the CPT omission errors showed such an anemic correlation with serum zinc when the parent/teacher ratings of inattention showed such a robustly significant correlation. CPT omissions have usually been accepted as a measure of inattention and would be expected to be rather collinear with parent and teacher ratings of inattention. It is possible that there was some kind of ceiling or floor effect. Because CPT is supposedly more objective than observer ratings, one begins wondering if parents and teachers were somehow influenced in their ratings by knowledge of the zinc levels ("unblinded"). However, this was not a treatment trial, neither parents nor teachers knew the zinc serum levels, and there was no reason for raters to focus on zinc levels even if they knew them, because they entered the study for other treatment and the zinc test was just incidental to the screening. Therefore, given the wide acceptance of parent and teacher ratings as valid severity/outcome measures in ADHD, we retain confidence in the validity of the ratings.

Another puzzling issue is the disconnect between the marginally low serum levels of zinc and the estimates of daily intake from the Food Frequency Questionnaire filled out by parents, which appeared adequate. There are three possible explanations besides chance: (1) The Food Frequency Questionnaire could be wrong; it is based on retrospective recall by an observer other than the subject and was adapted from an adult questionnaire, so that portions may have been overestimated somewhat; (2) There may be poor absorption of dietary zinc, either peculiar to ADHD or because of interaction with another nutrient; (3) There could be zincwasting metabolism, either associated with ADHD or in response to some dietary or other chemical stressor. The latter would be compatible with Ward's (1990, 1997) finding that in ADHD

children whose parents reported they were sensitive to food dyes, the serum zinc went down and urine zinc went up during the dye challenge. Although it was not specifically asked about, the parents of our sample did not mention dietary sensitivities.

Cautions and limitations

The data reported in this paper do *not* prove that zinc deficiency is “the cause of ADHD” nor that zinc supplementation would be an effective treatment for ADHD. They do not even conclusively prove that zinc is associated with inattention but not hyperactivity/impulsivity. A number of alternative explanations for the findings could be postulated. First, these could be chance findings. Secondly, this sample was limited to diagnosed ADHD. It is possible that inclusion of a broader spectrum of children would have yielded significant correlations of zinc levels with parent- and teacher-rated hyperactivity/ impulsivity and CPT commission errors.

Thirdly, zinc levels could just be markers for some other cause of ADHD, including poor general nutrition, rather than having a direct causative role. For example, they could be markers of essential fatty-acid deficiency or imbalance because series 2 prostaglandins, derived from polyunsaturated fatty acids, are believed to be necessary for zinc absorption (Song and Adham 1980). They could even be markers of general malnutrition; Wesnes et al. (2003) reported that a whole-grain cereal breakfast prevented the deterioration of schoolchild attention and memory over the morning that was permitted by no-breakfast and glucose-drink conditions. Furthermore, zinc levels could be markers of a gene that results in deficient zinc absorption or metabolism and also affects attention but not necessarily through the zinc deficiency. Finally, they could be markers for inflammation—either infection, trauma, or allergy. Zinc is reduced in acute inflammation (Shenkin 1995). Hagerman and Falkenstein (1987) reported twice the rate of otitis media in hyperactive children compared to controls, suggesting either immune problems or greater exposure to infectious agents. Infectious toxins, allergies or sensitivities, and repeated trauma from the increased accident rate in ADHD could all contribute to an association of low zinc levels with ADHD without making low zinc the cause of ADHD. In other words, the low zinc could be effect rather than cause.

Lastly, although this sample had carefully diagnosed ADHD of moderate to marked severity, it was not representative of ADHD clinical mental health samples because of the low rate of comorbidity. Most reports of ADHD comorbidity find approximately half with comorbid oppositional-defiant or conduct disorder and 25% or more with comorbid anxiety disorder. One likely explanation is the higher socioeconomic status of this sample, which was recruited by the advertisement for a trial of a nutritional supplement (not zinc). There was undoubtedly self-selection for families who were interested in nutritional treatment and who could tolerate the prospect of the 4 months of placebo to which half the participants would be assigned. The latter consideration alone could have excluded *de facto* those with the more severe conduct problems. However, the biasing of this sample to the higher socioeconomic classes and to the nutritionally conscious actually underscores the importance of the findings: Even this group, least expected to have marginal zinc deficiency and with a nutritionally adequate diet by the Food Frequency Questionnaire, showed an involvement of zinc levels in ADHD symptoms.

Clinical implications

The state of science in this area is not ready for immediate clinical application. In particular, there are not yet any data showing the effect of tolerable levels of zinc supplementation on measures of ADHD. (The Turkish trial by Bilici et al. used doses above the recommended upper tolerable limit, and the Iranian trial by Akhondzadeh et al. reported

considerable gastrointestinal symptoms from the sulfate form used there.) We and others are planning further trials. Zinc, though likely to be safe in recommended dietary allowance (RDA) amounts, is not entirely risk free: Toxicity and side effects at higher exposure (over 50 mg/day) have been reported. Furthermore, zinc alone may not be the answer, but a combination of nutritional considerations, for which zinc may be merely the tip of the iceberg. The issue calls for much more clinical research.

Conclusion

The data reported here suggest that zinc nutrition is involved in symptoms of inattention and, therefore, improving zinc nutritional status might improve inattentive symptoms. These remain largely untested hypotheses at present, but deserve research attention because of the obvious potential public health importance. Possible foci for future research are discussed in the companion review article (Arnold and DiSilvestro, 2005). The data available at this time do not prove that low zinc causes ADHD nor make zinc supplementation an established treatment.

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